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(54) Title: ANTIMICROBIAL COMPOSITION COMPOSED OF CONTROLLED RELEASE GLASSES

(57) Abstract

There is provided an antimicrobial composition for combatting infections. The material is a controlled release glass having two or more agents selected from the group consisting of metals, selenium and boron. Preferably the agents are selected from the group consisting of copper, silver, magnesium, zinc, cerium, manganese bismuth, selenium and boron. The combinations of copper and silver and of copper and zinc are particularly preferred and exhibit synergistic activity. The antimicrobial composition is effective against infections due to Proteus spp.

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ANTIMICROBIAL COMPOSITION COMPOSED OF CONTROLLED RELEASE GLASSES

The present invention relates to an antimicrobial material for combatting infections.

To combat infections at wound sites a variety of antibacterial agents have been incorporated into wound dressings. Some of these agents have been shown to have a deleterious effect on the delicate environment of a healing wound and may indeed retard the rate of wound healing. Individually, silver and copper are known to have useful biocidal properties (see Pyle et al, J. Appl. Bacteriology 1992. vol. 72, no.1, pp 71-79).

The use of glasses which can dissolve in water and body fluid and which are applied internally of the body are well-known. These glasses are formed from phosphorus pentoxide and may be modified to dissolve over a period of minutes, months or even years, as required. To date, such glasses have been used, in medicine, for the controlled release of a number of agents, for example, drugs, hormones and trace elements, but in each case the glass has been applied internally of the body to allow the agent to leach out into the body's circulatory system.

It is known that certain glasses, in which the usual glass former, silicon dioxide, of traditional glasses is replaced with phosphorus pentoxide as the glass former, are soluble in water and body fluids. The rate

of dissolution is controlled largely by the addition of glass modifiers such as calcium oxide. In simple terms, the greater the concentration of the modifier the slower is the rate of dissolution. The rates of dissolution which can be imparted to the glasses may range from minutes to months or even to several years. Soluble phosphate based glasses which have demonstrated good biocompatibility can incorporate inorganic metals such that a sustained release of the metals can be provided at the wound site.

Controlled release glasses (CRGs) which release silver ions to combat infections as described in WO-A-90/08470 of Giltech Limited, for example.

It has now been found that a combination of metal ions can, if suitably presented, reduce the amount of anti-microbial metal ions required to achieve bacteriostatic or bactericidal activity, whilst at the same time lowering the inflammatory response of the tissue.

The present invention therefore provides a method of combatting infection in a wound (such as microbial or fungal infection, for example bacterial, viral, or fungal infection) whilst maintaining cell viability, said method comprising providing a controlled release glass containing a combination of two or more agents selected from the group consisting of metals, selenium and boron. The agents are selected and combined together in concentrations sufficient to achieve bacteriostatic or bactericidal benefit. The concentrations of each agent is low enough to avoid cell death in the healing wound (for example due to protein binding etc) but in combination is sufficient to achieve at least bacteriostasis. By careful selection of the combination of agents used infection

can be combatted and wound healing promoted. In one embodiment the agents are selected from the group consisting of copper, silver, magnesium, zinc, cerium, manganese, bismuth, selenium and boron. Preferably at least one agent is silver, boron, bismuth, manganese, copper, cerium or zinc.

The present invention also provides a controlled release glass (CRG) composition for combatting infection in cells (such as microbial or fungal infection, for example bacterial or viral infection, including parasitic infections, for example bilharzia and blue/green algae) whilst maintaining cell viability. The glass controllably releases quantities of at least two agents selected from the group consisting of metals, selenium and boron; the combined concentration of released agents being sufficient to combat infections whilst aiding wound healing.

The controlled release glass according to the present invention comprises the agents set out above and in one embodiment the agents are selected from the group consisting of copper, silver, magnesium, zinc, cerium, manganese, bismuth, selenium and boron. Glasses containing silver as one agent are especially preferred. In particular combinations of copper and silver have been found to be particularly efficacious. Alternatively a glass containing combinations of copper and zinc or of magnesium and zinc are also suitable. Controlled release glasses of the type described in WO-A-89/01793 and WO-A-90/08470 are suitable as a means of presenting the agent combination.

The present invention also provides the use of a controlled release glass as described above in the manufacture of a medicament for combatting infection in

cells (such as microbial or fungal infection, for example bacterial or viral infection) whilst maintaining cell viability.

According to one embodiment of the present invention, the water-soluble glass comprises an alkali metal oxide M_2O, an alkaline earth oxide MO, phosphorus pentoxide P_2O_5 and said agents, for example silver and copper in elemental or salt form.

Most preferably, said glass contains not more than 40 mole % M_2O or MO, not less than 10 mole % M_2O or MO, and not more than 50 mole % nor less than 38 mole % phosphorus pentoxide, with the inclusion of 0.05 to 5.0 mole % of said agents (for example a silver salt, copper salt, magnesium salt and/or copper salt).

Said alkali metal oxide may be sodium oxide (Na_2O), potassium (K_2O) or a mixture thereof; and said alkaline earth oxide may be calcium oxide (CaO), magnesium oxide (MgO), or a mixture thereof.

The glass may also contain less than 5 mole % silicon dioxide (SiO_2), boric oxide (B_2O_3), sulphate ion (SO_4^{2-}), a halide ion, copper oxide (CuO) or a mixture thereof.

Typically the soluble glasses used in this invention comprise phosphorus pentoxide (P_2O_5) as the principal glass-former, together with any one or more glass-modifying non-toxic materials such as sodium oxide (Na_2O), potassium oxide (K_2O), magnesium oxide (MgO), zinc oxide (ZnO) and calcium oxide (CaO). The rate at which the glass dissolves in fluids is determined by the glass composition, generally by the ratio of glass-modifier to glass-former and by the relative proportions of the glass-modifiers in the

glass. By suitable adjustment of the glass composition, the dissolution rates in water at 38°C ranging from substantially zero to 25mg/cm^2/hour or more can be designed. However, the most desirable dissolution rate R of the glass is between 0.01 and 2.0mg/cm^2/hour. The water-soluble glass is preferably a phosphate glass. Silver may advantageously be introduced during glass manufacture as silver orthophosphate (Ag_3PO_4). The content of silver and other agents in the glass can vary in accordance with conditions of use and desired rates of release, the content of silver and other agents generally being up to 5 mole %. While we are following convention in describing the composition of the glass in terms of the mole % of oxides, of halides and of sulphate ions, this is not intended to imply that such chemical species are present in the glass nor that they are used for the batch for the preparation of the glass.

Boron may be present as a glass former within the glass itself, partially replacing phosphorus pentoxide. Generally the agents are added to the glass composition during glass manufacture, ie. in the melt. Alternatively, the glass may be preformed and the agent then introduced thereto.

The glass may be formed by a number of methods. It may simply be cast by conventional or centrifugal procedures, or it may be prepared via one or more stages of rod, fibre or tube drawing. Other preparation techniques include foamed glass or comminution of the glass followed by pressing and sintering into a solid body. It may be presented for example as a solid body, a powder or granules of preselected size, as flakes, or in the form of a number of hollow cylinders.

The glass composition according to the present invention may be used in any suitable form and mention may be made of powders, sinters, rods, sheets, beads and the like. Where the glass is to be used in finely divided form, it is possible for an admixture of two glasses to be prepared, each containing a single agent, and then to be combined in admixture to produce the composition according to the present invention. In one embodiment the glass may be in the form of a powder, as granules, as fibres that can be woven into a dressing form, as a sinter which may be shaped in a particular way, or cast into the required shape eg a collar to surround the area of penetration of a catheter into the body.

When combined with a carrier the glass may be used as a filler in polymers for surface release eg in silicones, natural and synthetic rubbers and medical plastics and polymers.

Alternatively, the glass may be incorporated in the adhesive of adhesive film dressings, in lint, wool, tow and gauze dressings and as part of wound management products such as foam, hydrogels and hydrocolloids, films, gels and creams.

Combinations of these examples can also be used.

The present invention will now be further described with reference to the following, non-limiting, examples.

EXAMPLE 1

In this study a comparison of the in vitro cytotoxic effect of various antibacterial agents is made by means of mammalian cell culture with MTT (3-(4,5-dimethylthiazol-2-yl)-2,5,-diphenyltrazolium bromide) assay.

Materials and Methods

The materials used were controlled release glasses containing silver, copper, magnesium and zinc ions, chlorhexidine diacetate salt (CHD), Iodoform (0.9wt% iodine) and polyvinylpyrrolidone iodine complex with 11.4% available iodine (PVP). It has been shown that the biocidal effects of silver, copper and iodine occur at the levels of 10, 110 and 200 parts per billion (ppb) respectively. A range of exudates/solutions were prepared in the following concentrations, 1, 10, 100, 250, 500 and 1000 ppb, with sterile distilled water and double strength cell culture medium.

The L929 mouse fibroblasts were placed in 96 well plates, each well containing 1 x 10^5 cells suspended in 200μl of cell culture medium with 5% foetal calf serum, and incubated at 37°C/5% carbon dioxide for 48 hours. The cell culture medium was removed and replaced with the prepared exudates/solutions. The control was a solution of 50% double strength cell culture medium and 50% sterile (PBS). The plates were then incubated for time periods of 24, 48 and 72 hours following which the MTT assay was carried out using a standard procedure.

Results

After 24 hours, apart from chlorhexidine (CHD), no

material had a deleterious effect on the growth of the cells up to a concentration of 1000ppb. The controlled release glasses containing Cu, Mg and Zn ions all seem to have the effect of increasing the metabolic rate of the cells after 48 hours and the effect is seen further at 72 hours with Cu at all levels above 10ppb.

With increasing time the CHD causes cell death at just 100ppb. The Ag releasing glass inhibited cell growth at 48 hours but after a further 24 hours the number of viable cells present is comparable with the other ion releasing glasses. The detrimental effect of Iodoform and PVP on cell activity is not seen until 1000ppb and upto this point resemble the profile of the Ag glass.

Conclusion

It can be seen that the controlled metal ion releasing glasses sustain cell growth, if not increase the rate of cell division, whereas the antibacterial agent chlorhexidine produces irreversible cell damage at low concentrations.

As the glasses are releasing the metal ions they will become available over a period of time and therefore the levels of the ions will be lower initially. This may explain why the Cu and Ag ions did not kill all the cells at 1000ppb.

EXAMPLE 2

The MTT assay is now widely used in the evaluation of biomaterials, and is becoming the standard in vitro test method for use in examining extracted or soluble samples.

The cell line used for this study was the established L929 mouse fibroblast, grown in standard culture medium supplemented with 10% foetal calf serum.

The following materials were examined

Materials used:
- CRG/Ag
- CRG/Cu
- Chlorohexidine (CHD)
- Polyvinylpyrolidone (PVP)
- Iodoform

The compositions of the silver and copper glasses (CRG/Ag and CRG/Cu respectively) were as follows:

Silver Glass (CRG/Ag):	Component	Mole %
	Na_2O	34
	CaO	15
	Ag_2O	3
	P_2O_5	48

The solution rate was 2.74 mg/cm^2/hour at 37°C.

Copper Glass (CRG/Cu):	Component	Mole %
	Na_2O	32
	CaO	15
	CuO	5
	P_2O_5	48

The solution rate was 1.54 mg/cm^2/hour at 37°C.

The antiseptic agents and controlled release glasses were added to sterile distilled water to give a concentration of 2000ppb, and stored before use 4°C.

The fibroblast cells were suspended in culture medium and aliquoted into 96 well plates, to a cell density of approximately 50,000 cells/mL, 500μL were placed in each well. The plates were incubated for 2 days at 37°C to near confluence.

After this time period dilutions of all materials were prepared at concentrations of 1000, 500, 250, 100, 10 and 1 ppb with cell culture medium. The original cell culture medium was removed from the plates and 100μL/well of these dilutions were added to each plate as detailed below. Controls were prepared from 1 part double strength cell culture medium to 1 part sterile PBS.

The solutions were incubated with the cells for 24 hours at 37°C. After this time period the MTT salt was prepared at a concentration of 5mg/ml. The material dilutions were removed from the plates and 100μL/well of MTT salt added. The plates were then incubated for 4 hours. During this period viable cells will clause a reduction of tetrazolium to formazan producing a blue crystal formation. Thus the intensity of the blue is directly related to the number of activity of the cells. The MTT solution was then removed and 50μL/well of isopropanol was added to each plate and left for 20 minutes. The isopropanol is used to release the dye which was formed within the viable cells.

The optical densities of all the solutions in the plates were then measured using and ELISA plate reader. The results set out in Figure 1 to 8 were obtained.

EXAMPLE 3

Glass compositions each containing a single agent of interest were individually tested against a range of micro-organisms by placing a bead of the test glass in the centre of an agar plate which is then innoculated with bacteria to cultivate a continuous lawn. The size of the zone of inhibition produced around each sample was measured and recorded. The zone size is proportional to the antibacterial activity of each composition, since the agent present in the glass gradually diffuses out into the surrounding agar and affects bacterial growth in that area. It is expected that the active agents diffuse further than indicated by the outer edge of the zone, but in concentrations too low to cause antibacterial activity.

The sensitivity tests were conducted on isosens agar plates each with a standard depth of agar. The agar plates were used within 4 days of preparation and were stored in a cold room (4°C) until use.

Glass compositions containing a metal ion (selected from silver, copper, magnesium and zinc) were prepared. The silver and copper glasses are as described in Example 2. Each glass was tested against the following micro-organisms: *Candida albicans, Staphylococcus aureus, E. Coli, Pseudomonas areuginosa, Enterococcus* and a randomly selected strain of *Proteus spp.*

After 24 hours, 48 hours and 72 hours the zones were measured and the results are set out in Table 1.

Table 1

Test Organism	Incubation Time (Hrs)	Zone Size (mm)			
		Ag	Cu	Mg	Zn
Pneumococcus	24	11	11	NT	NT
	48	8	10	NT	NT
	72	5	9	NT	NT
Enterococcus	24	2	6	0	0
	48	2	5	0	0
	72	0	4	0	0
Staph aureus	24	4	6	0	0
	48	3	6	0	0
	72	3	4.5	0	0
Proteus sp.	24	1.5	9	2	4.5
	48	1.5	8	2	0
	72	1.5	4	2	0
E coli	24	5	9	0	3
	48	3	8	0	2
	72	2	6	0	1
Pseudomonas	24	4	9	3	3
	48	3	7	2	0
	72	3	5	2	0
Candida alb.	24	3	5	0	2.5
	48	0	5	0	0
	72	0	5	0	0

Once the zone sizes were established, pairs of agents were tested together. The two beads of glass were placed a specific distance apart on a single prepared agar plate, the distance between the beads was the total of their respective zone sizes at 24 hours minus 2mm. After 24 hours the microbial growth was examined. Particular attention was paid to the area where the zones of antibacterial activity converged. Here the area of microbial growth tapers down to a fine point. Where microbial growth between the beads was completely prevented it was concluded that the combination of agents had a synergistic action.

A combination of copper and silver and a combination of copper and zinc were found to exhibit enhanced activity, particularly against Proteus sp.

The Example was repeated, with the spacing of the beads being the sum of the respective zones sizes of the agents at 24 hours. The same combinations were found to be particularly effective, and the antibacterial activity observed was still evident after 72 hours.

CLAIMS

1. A controlled release glass composition for combatting infection in cells whilst maintaining cell viability, said glass being able to controllably release quantities of at least two agents selected from the group consisting of metals, selenium and boron; the combined concentration of released agents being sufficient to combat infections whilst aiding wound healing.

2. A composition as claimed in Claim 1 wherein said agents are selected from the group consisting of copper, silver, magnesium, zinc, cerium, bismuth, manganese, selenium and boron.

3. A composition as claimed in Claim 2 containing at least one agent selected from the group consisting of silver, boron, bismuth, cerium, manganese, copper and zinc.

4. A composition as claimed in any one of Claims 1 to 3 containing silver.

5. A composition as claimed in Claim 4, wherein said agents are silver and copper; zinc and copper; or magnesium and zinc.

6. A composition as claimed in Claim 5, wherein said agents are silver and copper.

7. A method of combatting infection in a wound whilst maintaining cell viability, said method comprising providing a controlled release glass as claimed in any one of Claims 1 to 6.

8. A method as claimed in Claim 7 wherein said infection is due to *Proteus spp.*.

9. The use of a controlled release glass as claimed in any one of Claims 1 to 6 in the manufacture of a medicament for combatting infection in cells whilst maintaining cell viability.

10. The use as claimed in Claim 9 wherein said infection is due to *Proteus spp.*.

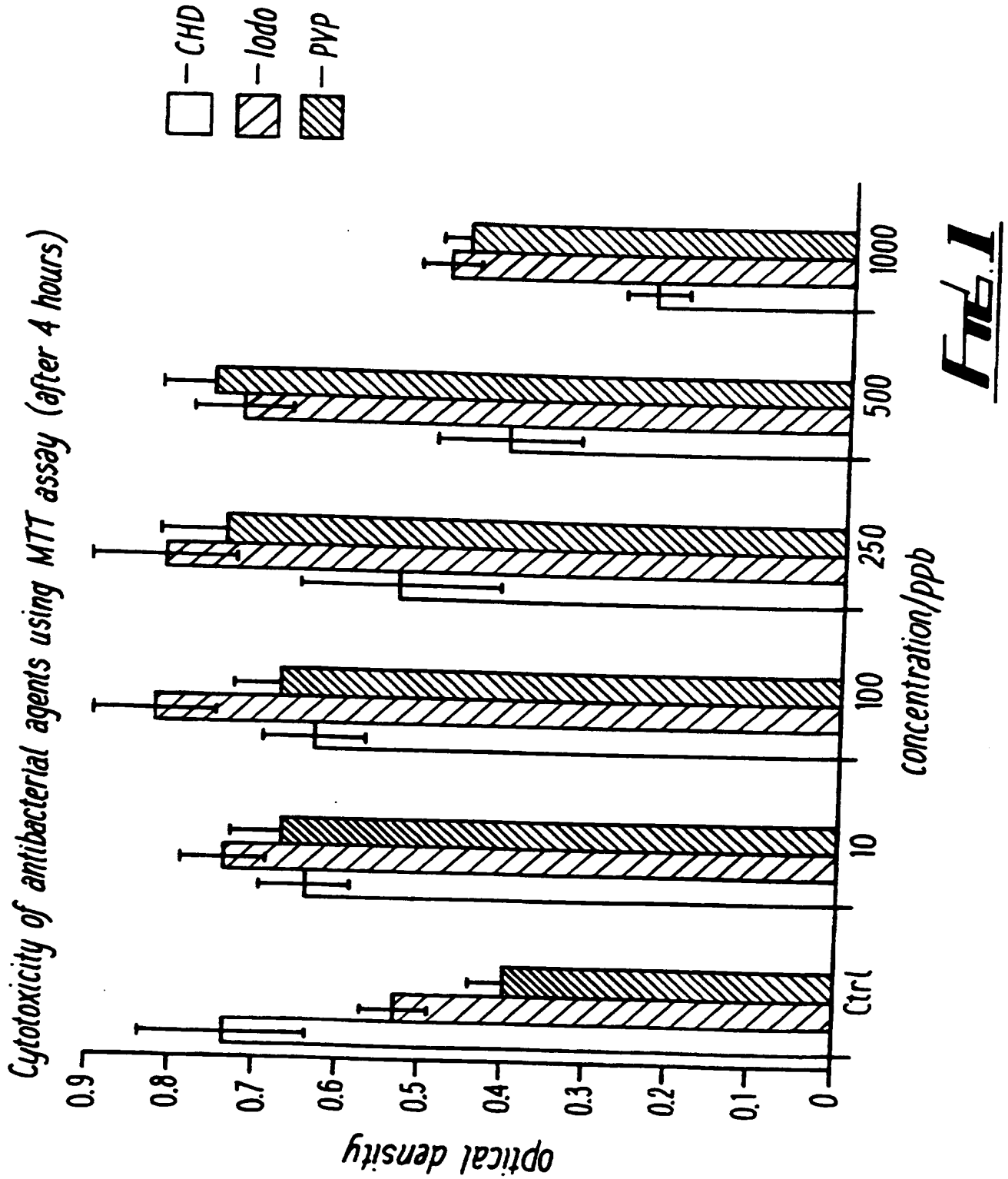

Fig. 1

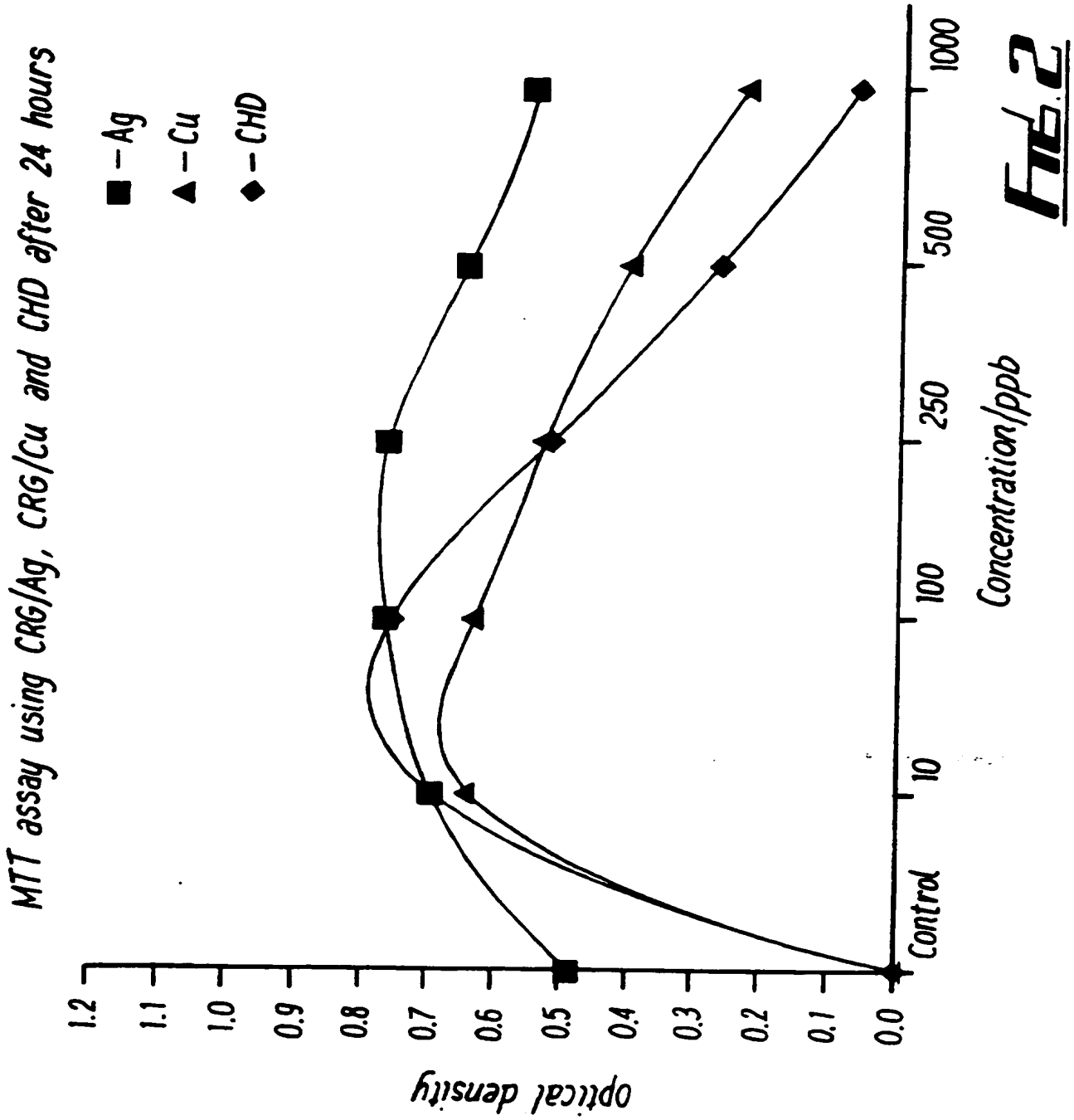

Fig. 2

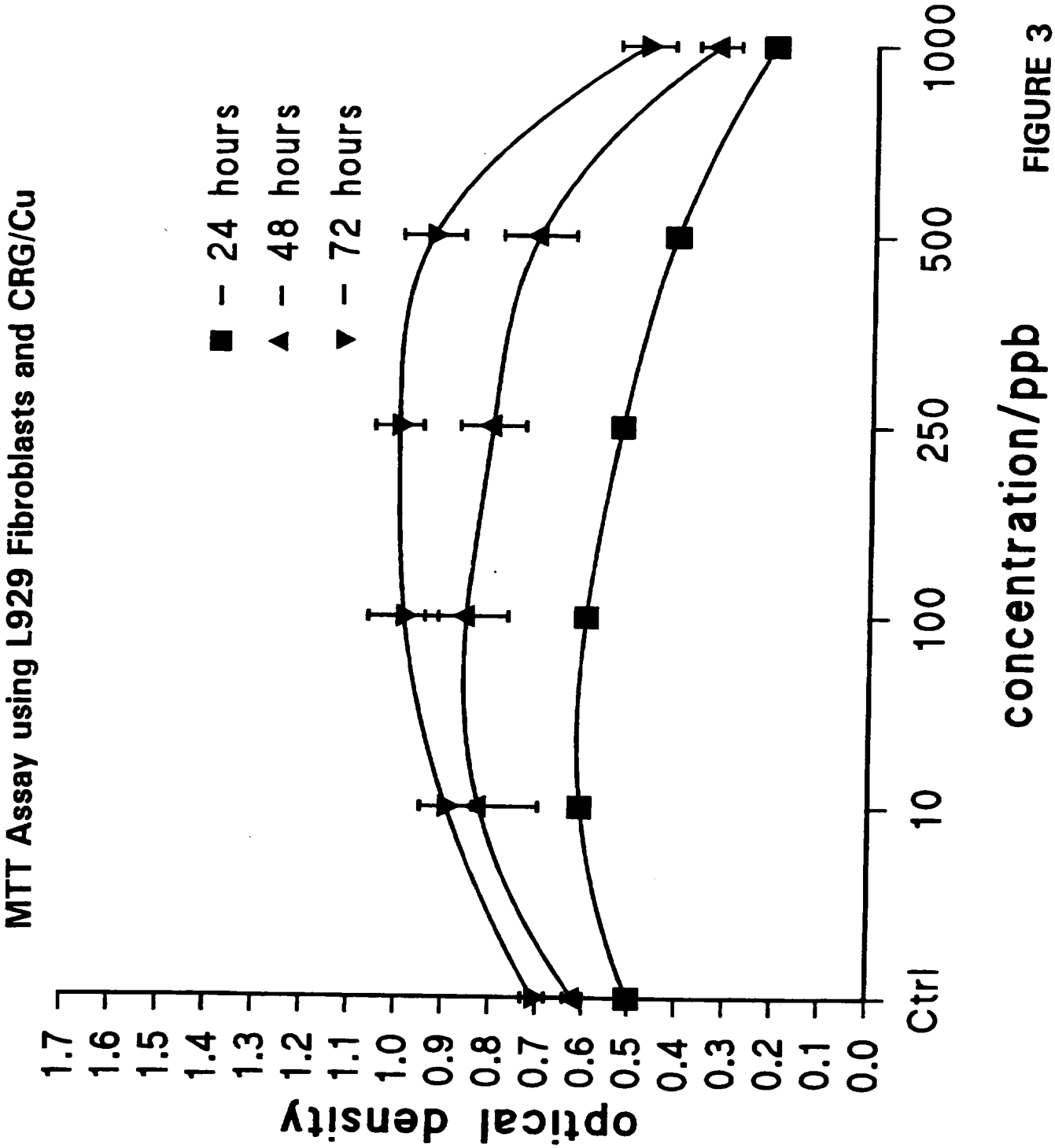

FIGURE 3

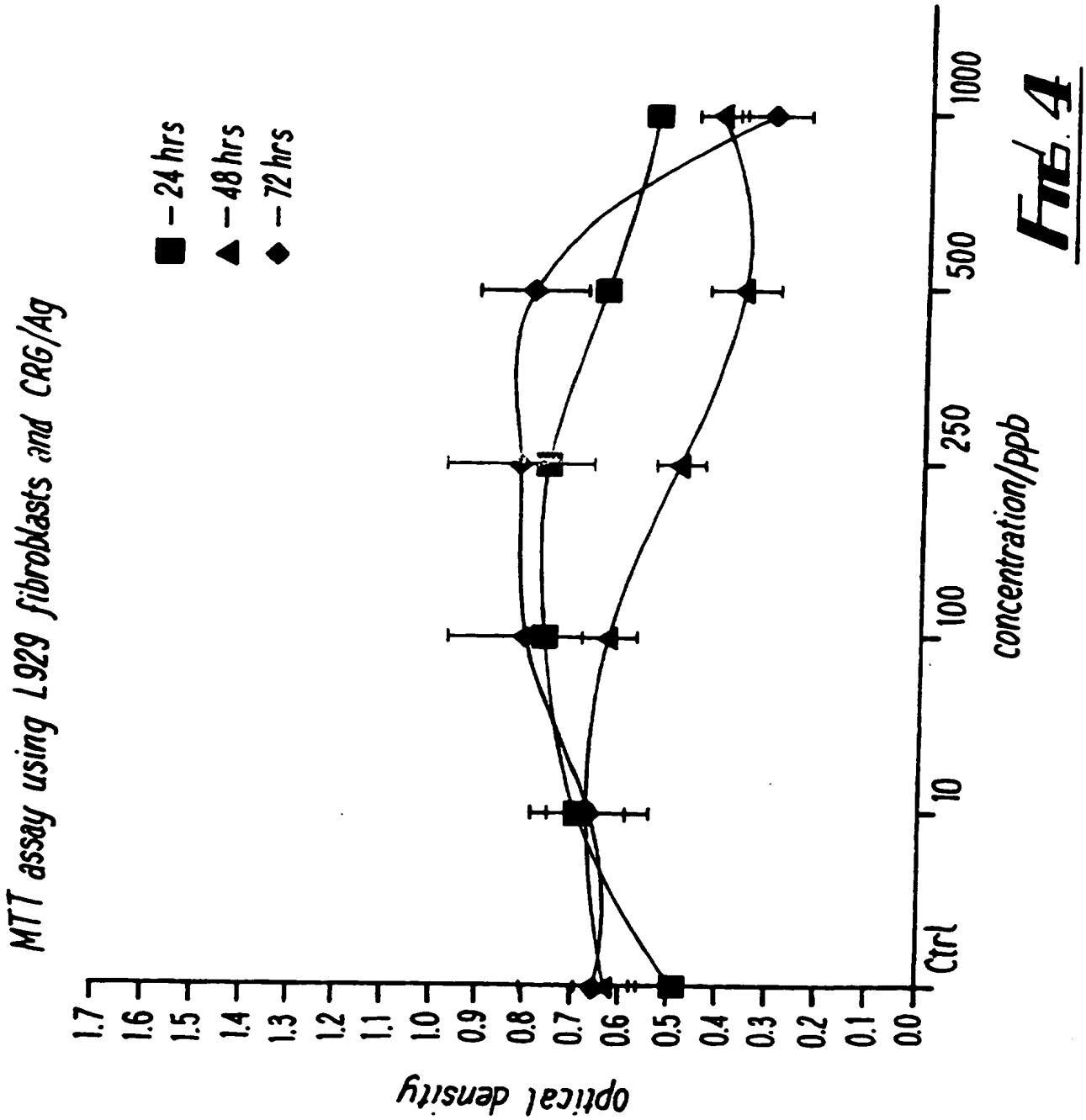

Fig. 4

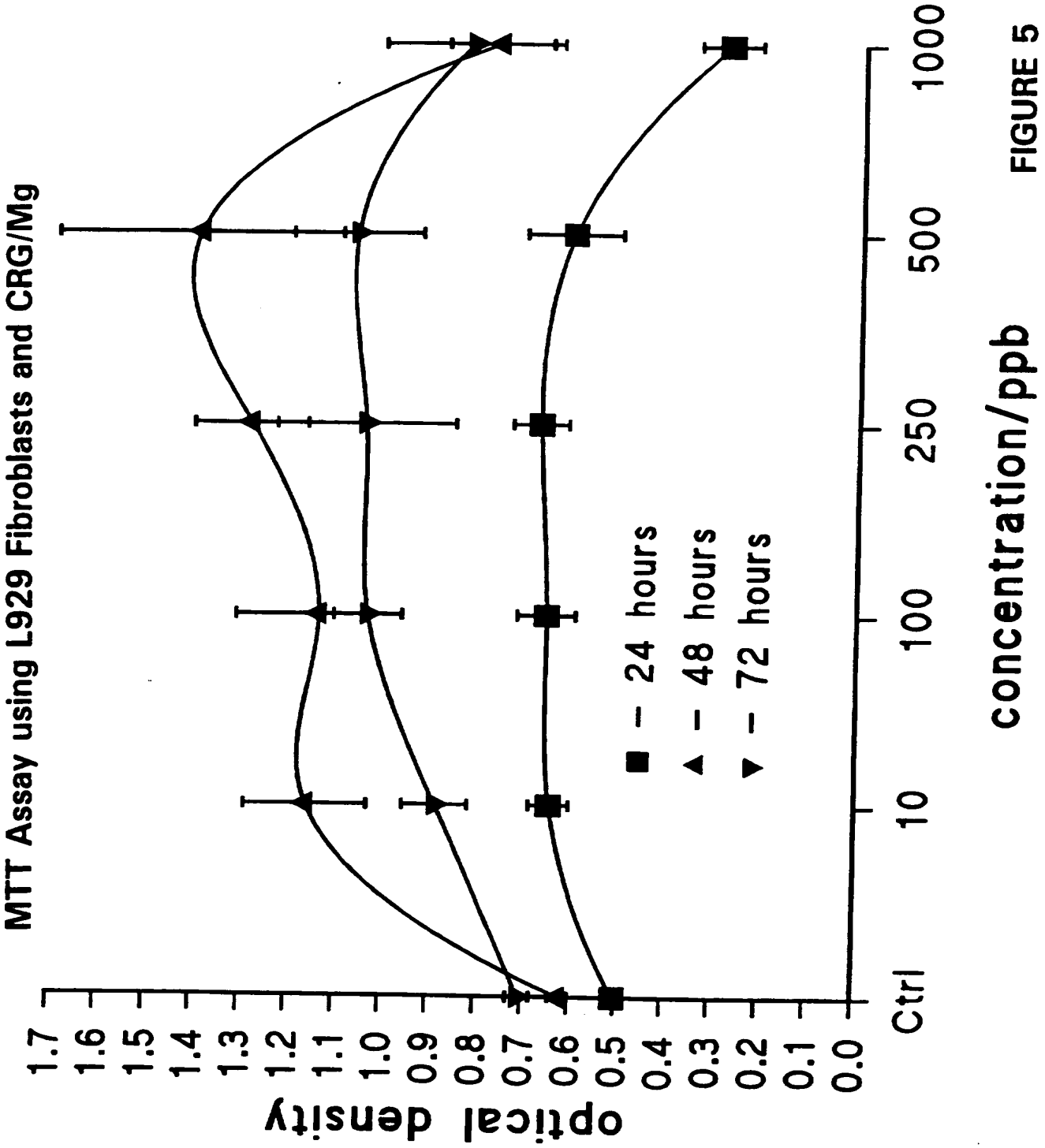

FIGURE 5

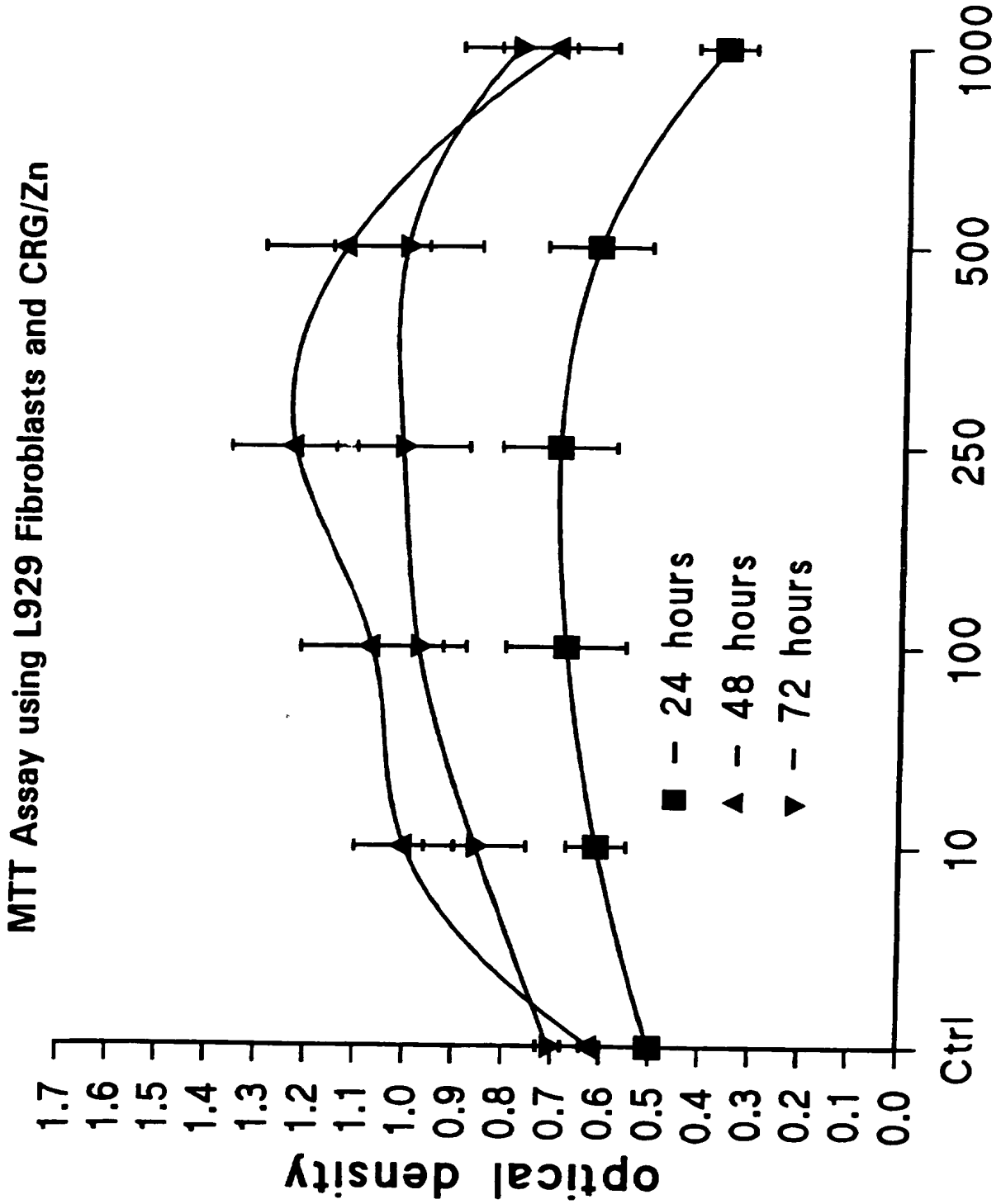

FIGURE 6

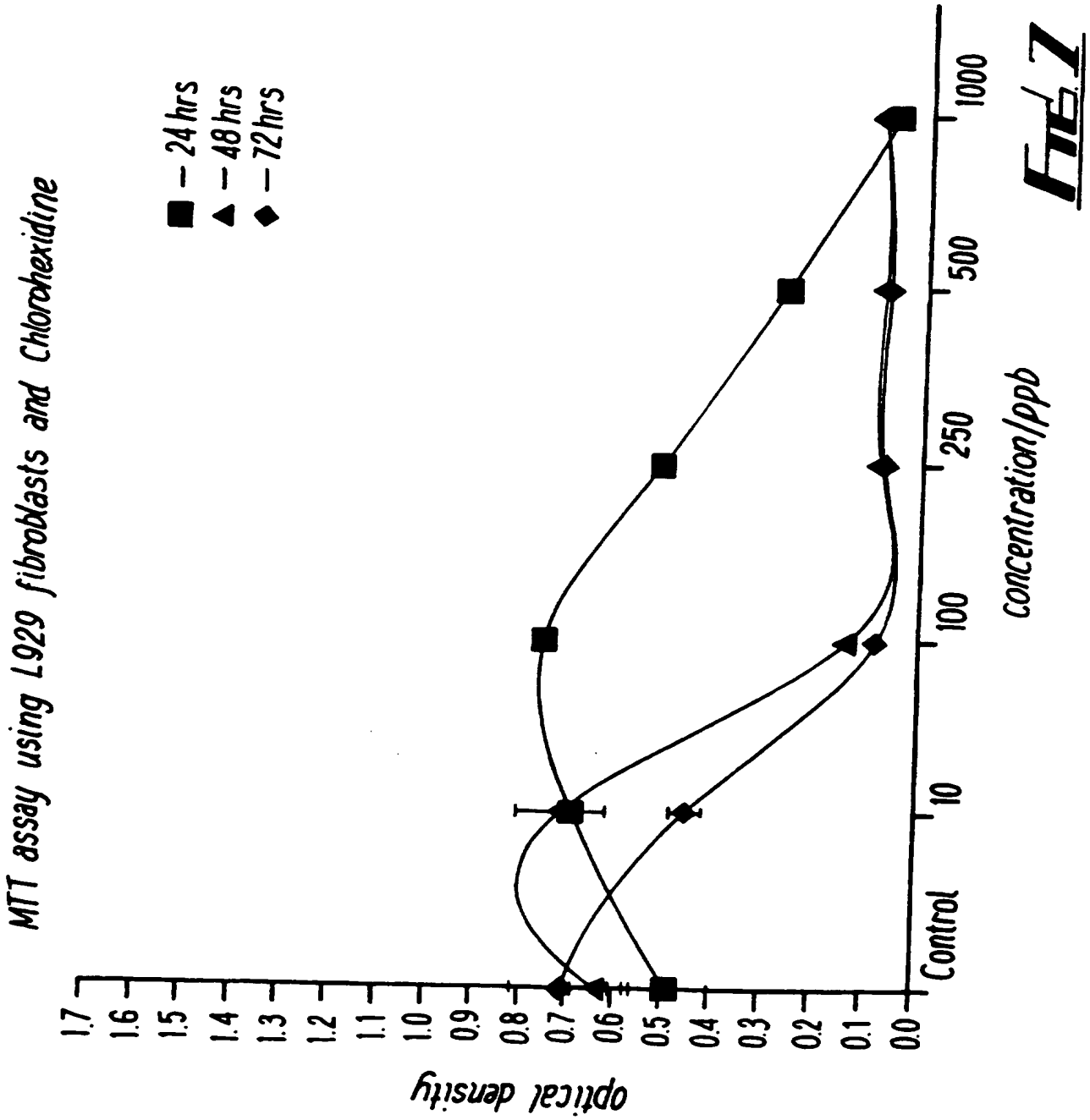

Fig 7

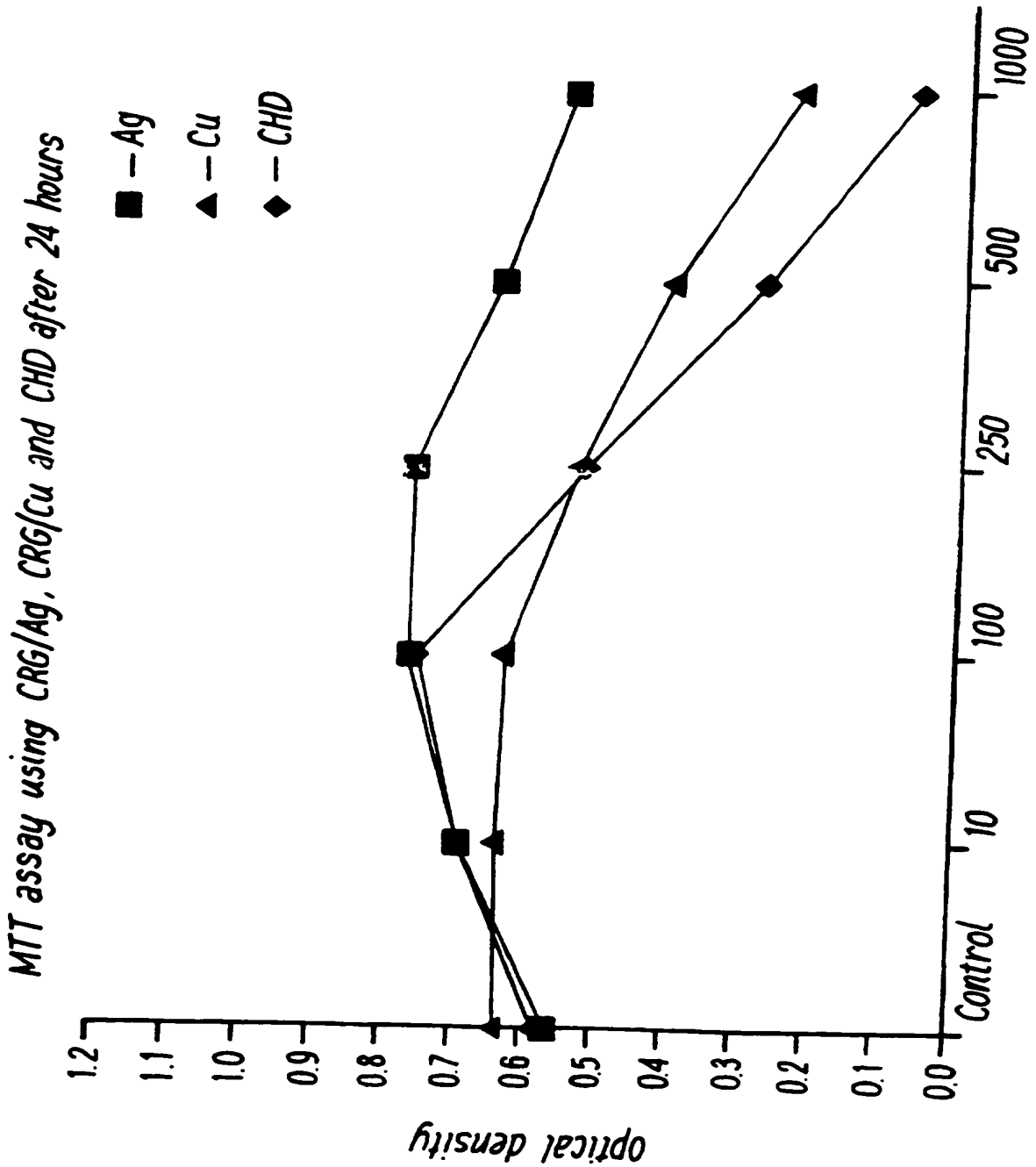

Fig. 8

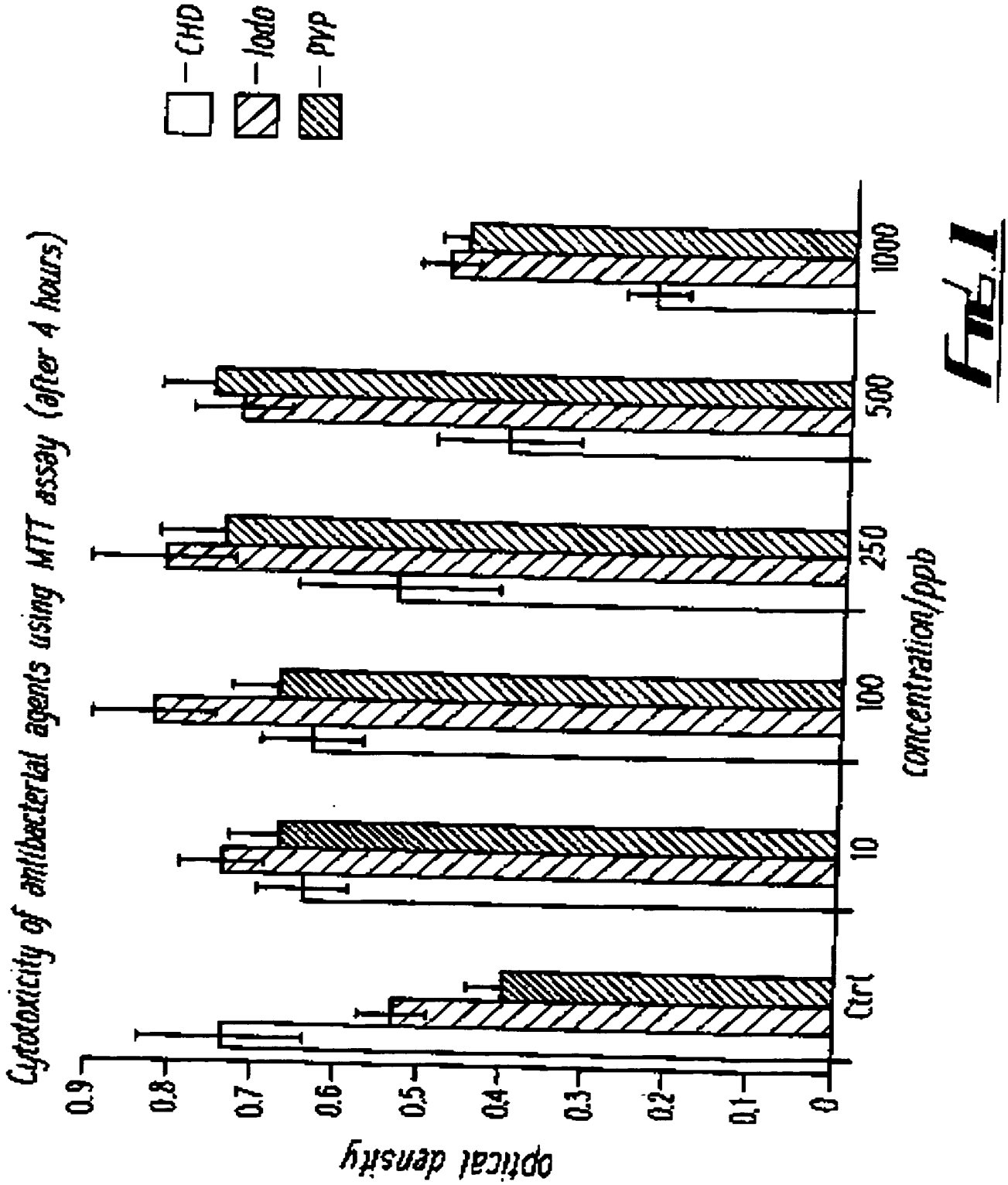

Fig. 1

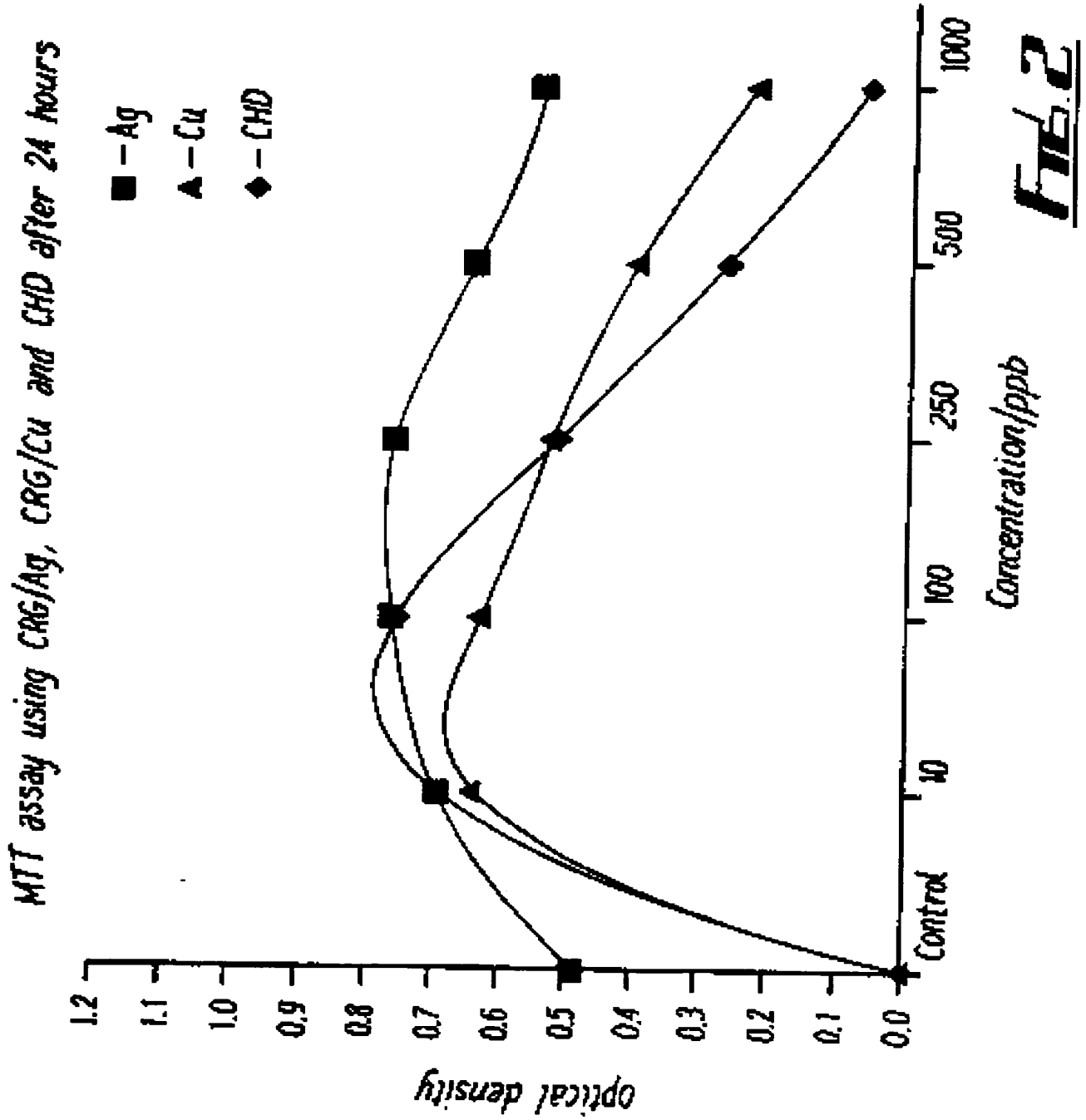

Fig.2

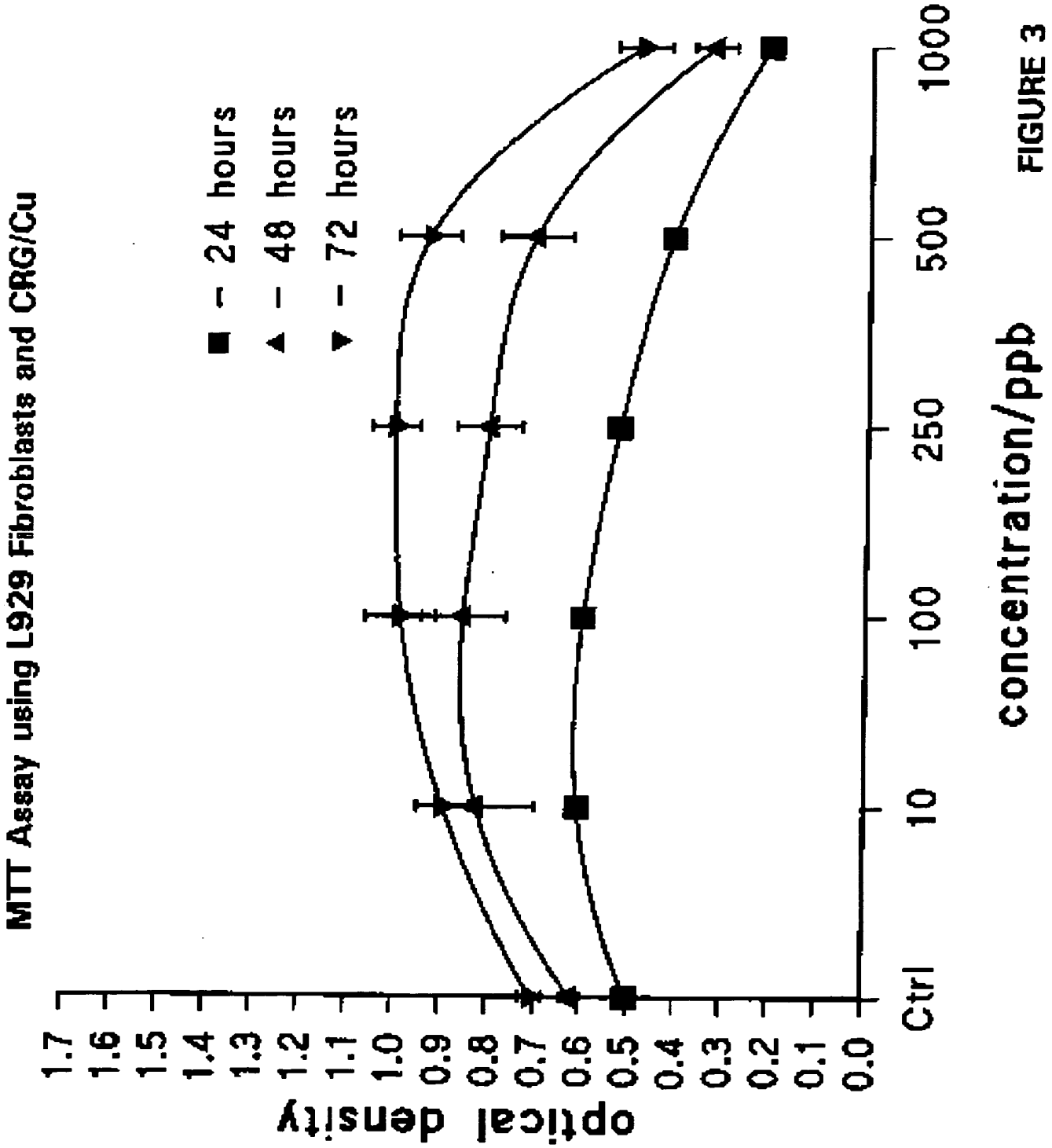

FIGURE 3

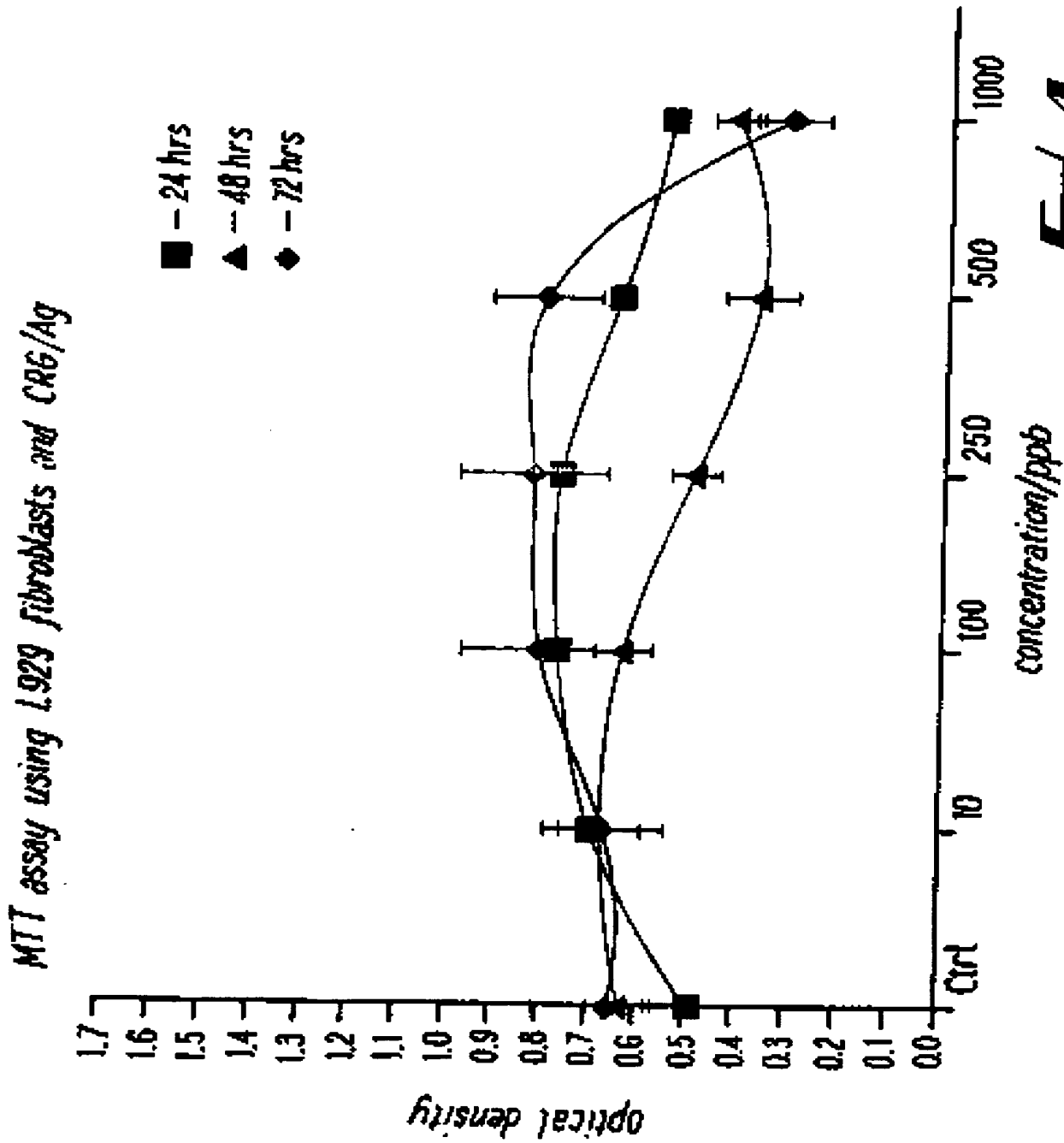

Fig 4

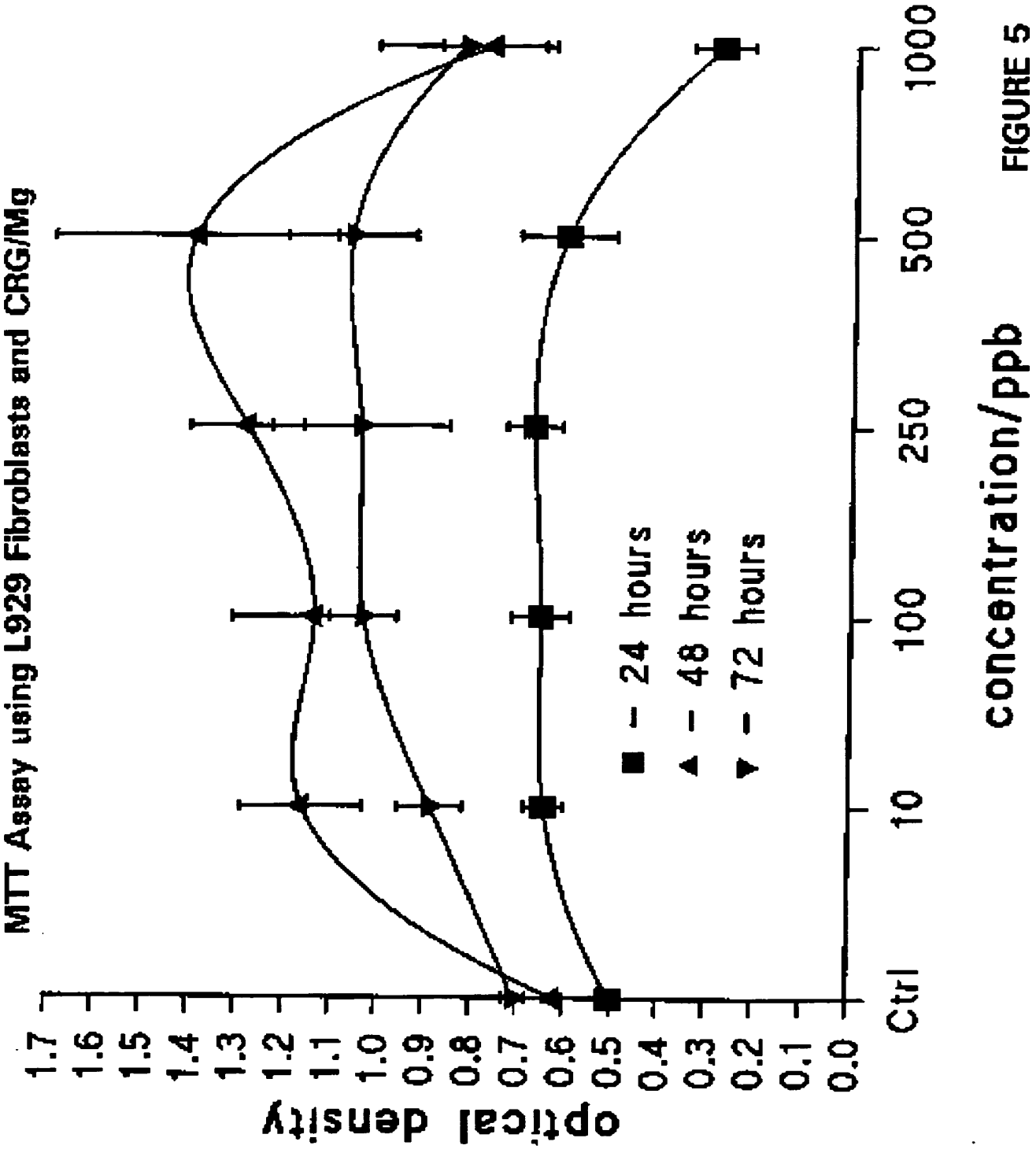

FIGURE 5

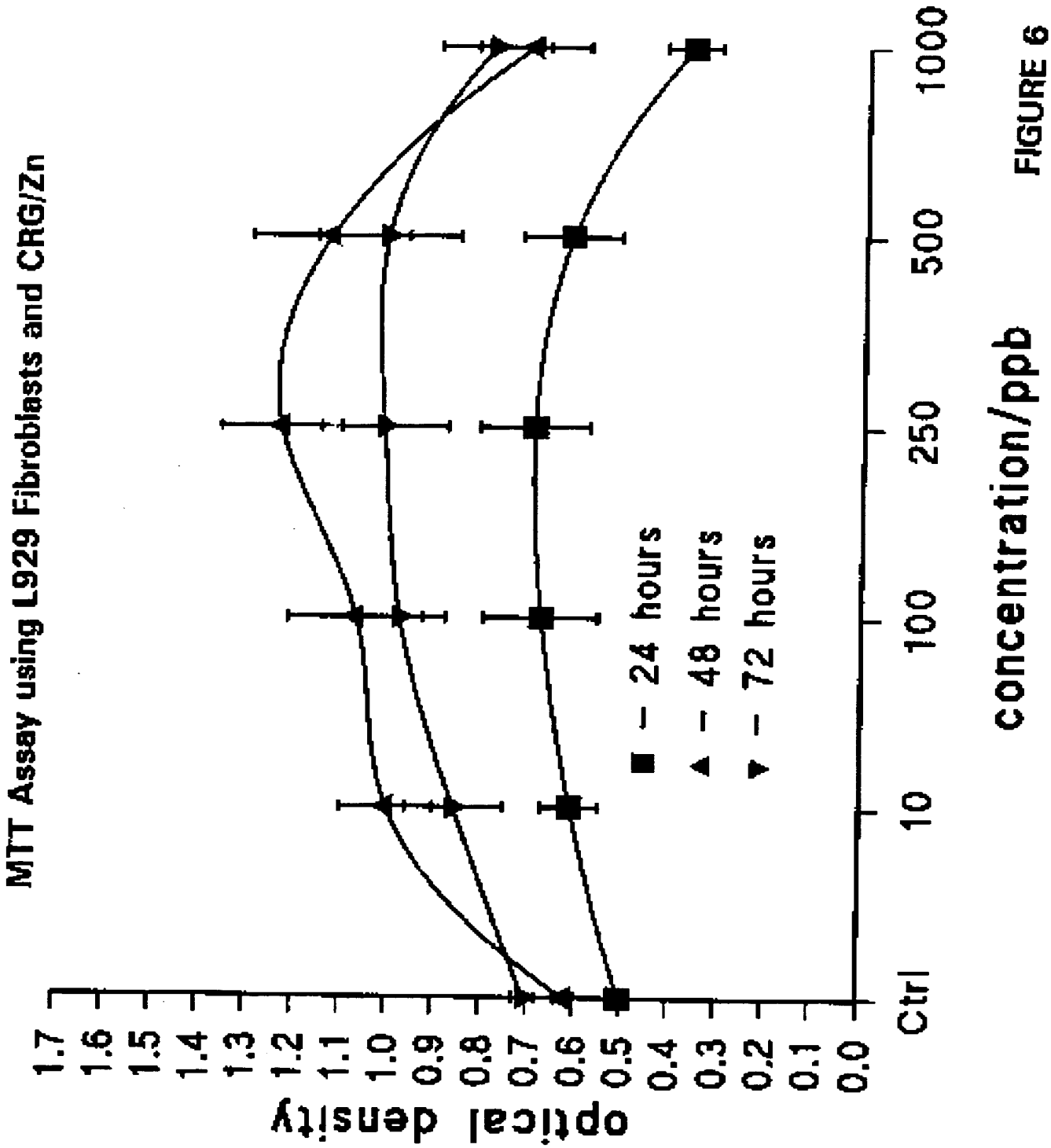

FIGURE 6

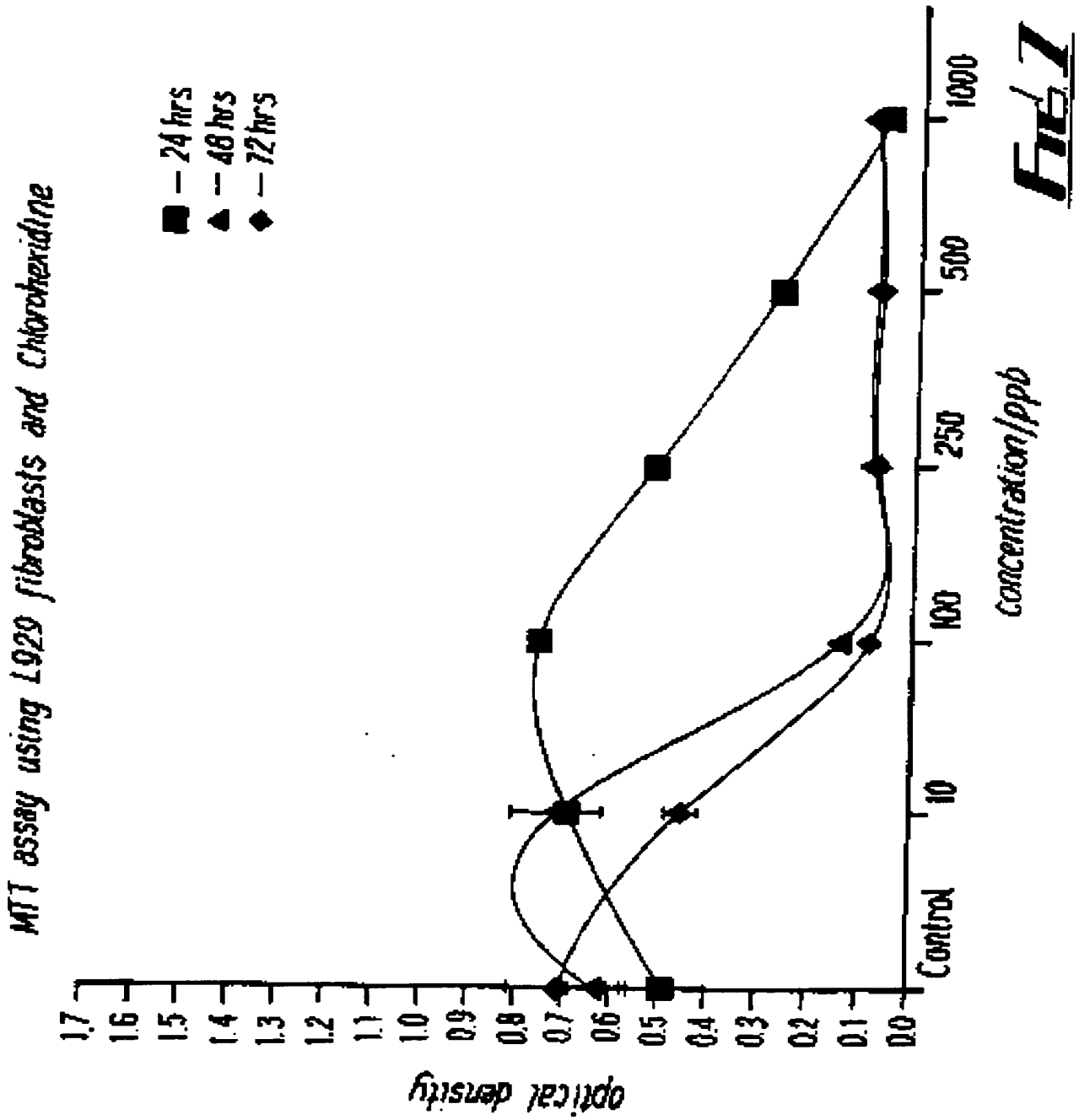

Fig 7

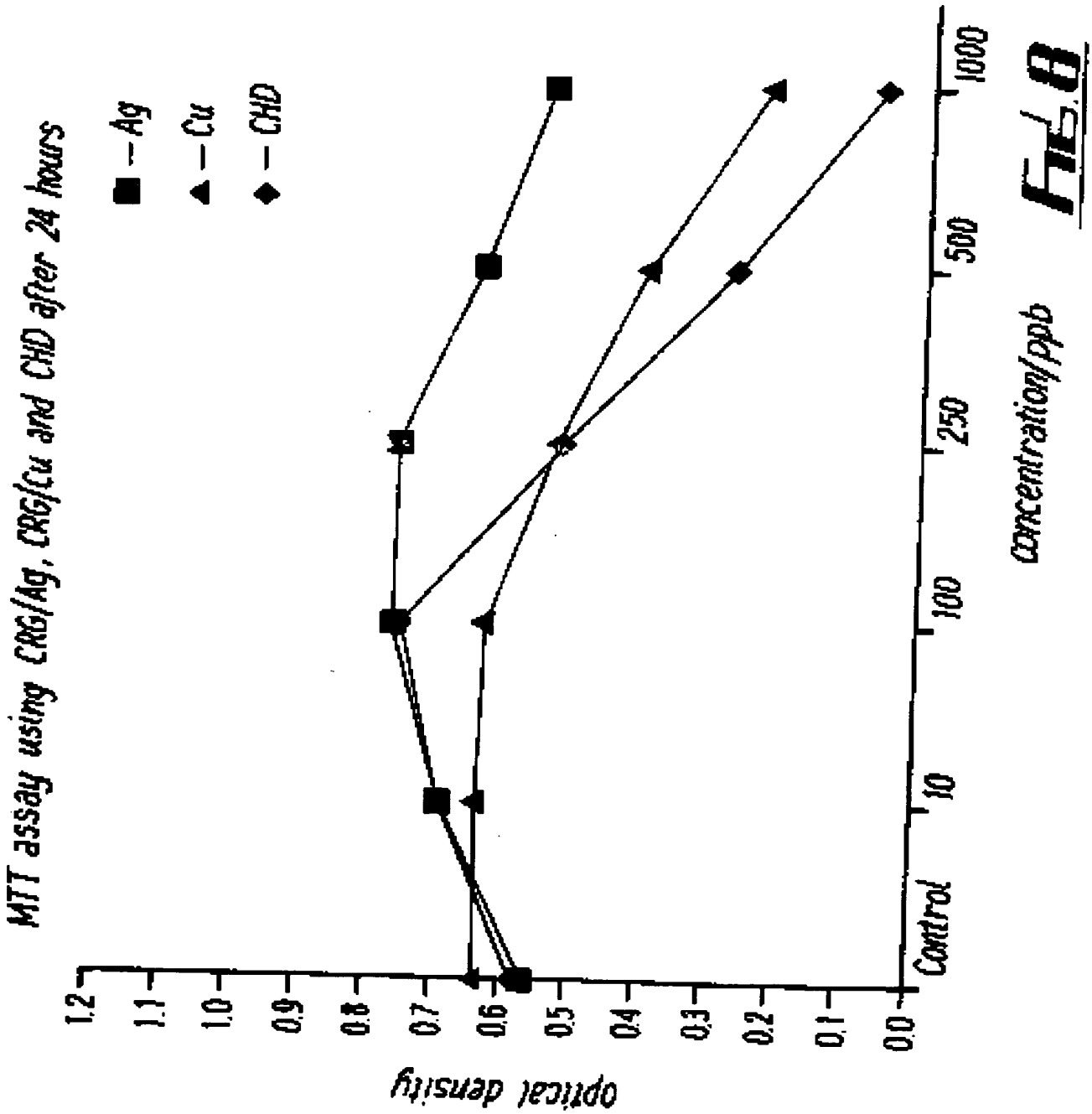

FIG. 8

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Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
26 September 1996 (26.09.96)

(54) Title: ANTIMICROBIAL COMPOSITION COMPOSED OF CONTROLLED RELEASE GLASSES

(57) Abstract

There is provided an antimicrobial composition for combatting infections. The material is a controlled release glass having two or more agents selected from the group consisting of metals, selenium and boron. Preferably the agents are selected from the group consisting of copper, silver, magnesium, zinc, cerium, manganese bismuth, selenium and boron. The combinations of copper and silver and of copper and zinc are particularly preferred and exhibit synergistic activity. The antimicrobial composition is effective against infections due to Proteus spp.

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INTERNATIONAL SEARCH REPORT

tional Application No
PCT/GB 96/00267

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K33/38 A61K33/34 A61K33/32 A61K33/30 A61K33/24
A61K33/22 A61K33/06 A61K33/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 014, no. 115 (C-0696), 5 March 1990 & JP,A,01 317133 (MITSUBISHI RAYON ENG CO LTD), 21 December 1989, see abstract --- -/--	1-7,9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
19 July 1996	29.07.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Kanbier, D

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 9048 Derwent Publications Ltd., London, GB; AN 90-358041 XP002008945 & JP,A,02 258 256 (ASAHI CHEMICAL IND KK) , 19 October 1990 see abstract & PATENT ABSTRACTS OF JAPAN vol. 015, no. 008 (M-1067), 9 January 1991 & JP,A,02 258256 (ASAHI CHEM IND CO LTD), 19 October 1990, see abstract	1-4,6,7, 9
X	PATENT ABSTRACTS OF JAPAN vol. 017, no. 251 (C-1060), 19 May 1993 & JP,A,05 001226 (ISHIZUKA GLASS CO LTD), 8 January 1993, see abstract & DATABASE WPI Week 9306 Derwent Publications Ltd., London, GB; AN 93-049740 & JP,A,05 001 226 (ISHIZUKA GLASS KK) , 8 January 1993 see abstract	1-7,9
X	PATENT ABSTRACTS OF JAPAN vol. 015, no. 369 (C-0868), 18 September 1991 & JP,A,03 146436 (U H I SYST KK), 21 June 1991, see abstract	1-7,9
X	GB,A,2 164 557 (STANDARD TELEPHONES PLC) 26 March 1986 see page 1, left-hand column; table 13 see claims 1,7,12,13,19,21; table 16	1-3,5,7
X	GB,A,2 163 346 (UNIV LEEDS IND SERVICE LTD) 26 February 1986 see page 1, left-hand column, line 47 - right-hand column, line 85; claims 1,6,7	1-3,5,7
A	INFECTION, vol. 17, no. 2, 1989, MUNICH, pages 81-85, XP000576802 SOEDERBERG ET AL: "The effects of an occlusive zinc medicated dressing on the bacterial flora in excised wounds in the rat" see page 84, right-hand column; tables 1,2	5,7,8,10

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HYGIENE + MEDIZIN, vol. 6, no. 9, 1981, pages 389-398, XP002008944 SCHMIDT-LORENZ: "ANTIMICROBIAL TREATING OF PARTICULATE FILTERS MADE OF MICROGLASS ... PROPERTIES. PART I: MICROBIOSTATIC EFFECTIVENESS" see page 397; table 1 ---	1-4,6
A	JOURNAL OF MATERIALS SCIENCE, vol. 6, no. 12, 1995, pages 853-856, XP000576120 SHERIDAN ET AL: "THE EFFECT OF ANTIBACTERIAL AGENTS ON THE BEHAVIOUR OF CULTURED MAMMALIAN FIBROBLASTS" see page 856, right-hand column ---	1-4,7,9
A	DATABASE WPI Week 9416 Derwent Publications Ltd., London, GB; AN 94-131942 XP002008946 & JP,A,06 080 527 (SHOKUBAI KASEI KOGYO KK) , 22 March 1994 see abstract -----	1-4,7,9

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INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/GB96/00267

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 7-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

tional Application No
PCT/GB 96/00267

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		AU-B-	4733085	20-03-86
		EP-A-	0178763	23-04-86
		US-A-	4662879	05-05-87
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		AU-B-	1135783	01-09-83
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		FR-A-	2521835	26-08-83
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		JP-A-	58158140	20-09-83
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		US-A-	4482541	13-11-84